The Use of Noninvasive Optical Coherence Tomography to Monitor the Treatment Progress of Vismodegib and Imiquimod 5% Cream in a Transplant Patient with Advanced Basal Cell Carcinoma of the Nose

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ABSTRACT

Immunosuppressed transplant recipients have increased risk for the development of basal cell carcinoma skin cancers. While oral vismodegib therapy has been successful in treating locally advanced basal cell tumors, few studies document its use and efficacy in organ transplant patients. In this immunocompromised population, topical imiquimod 5% cream has been shown to be an effective and well-tolerated option for superficial and nodular basal cell carcinomas. To the authors' knowledge, no data documents the use of optical coherence tomography, a noninvasive imaging technique, to monitor progress of such combined therapies on *in vivo* skin. The authors report the successful treatment of an extensive basal cell carcinoma on the nose of an immunosuppressed 54-year-old Caucasian man with a history of kidney and pancreas transplantations. By combining continuous noninvasive lesion monitoring with vismodegib 150mg/d therapy and adjuvant imiquimod 5% topical cream, the patient showed complete disease clearance on clinical, optical coherence tomography, and histological evaluation. This report supports the feasibility and efficacy of nonsurgical treatment of basal cell lesions in complicated transplant patients and the need for individualized treatment plans. A noninvasive follow-up tool, especially during nonsurgical therapy, is of critical value to ensure the best possible treatment outcome for the patient. (*J Clin Aesthet Dermatol.* 2016;9(8):37–41.)

Basal cell carcinoma (BCC) is the most common malignancy in individuals of mixed European descent, and accounts for approximately 80 percent of all skin malignancies.[1–3] The risk for developing BCC is greatly increased in organ transplant recipients who use a combination of immunosuppressive drug therapies for prolonged periods of time.[4–6] BCC is the second most frequent skin cancer associated with immunosuppression and more commonly metastasizes in this population than patients who have human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) or iatrogenic immunodeficiency.[4,6,7] The management of extensive BCC in immunosuppressed organ transplant recipients can be a challenge for dermatologists.

The current gold standard of diagnosis and management of extensive and infiltrative BCC is clinical and histopathological evaluation followed by surgical excision.[3] Such invasive procedures often lead to poor cosmetic outcomes and/or functional impairment[8] and there has been increased focus on alternative nonsurgical diagnostic, follow-up and treatment modalities for these patients.

Optical coherence tomography (OCT), a noninvasive imaging technique, allows for real-time detection and assessment of skin lesions. OCT uses near-infrared light to generate high-resolution black and white cross-sectional images of tissue micro-architecture down to a depth of 2mm.[9–12] These images depict cellular components in the same plane as traditional histological cuts, and studies have established that they are sufficiently detailed for identification of morphological criteria for BCC and other

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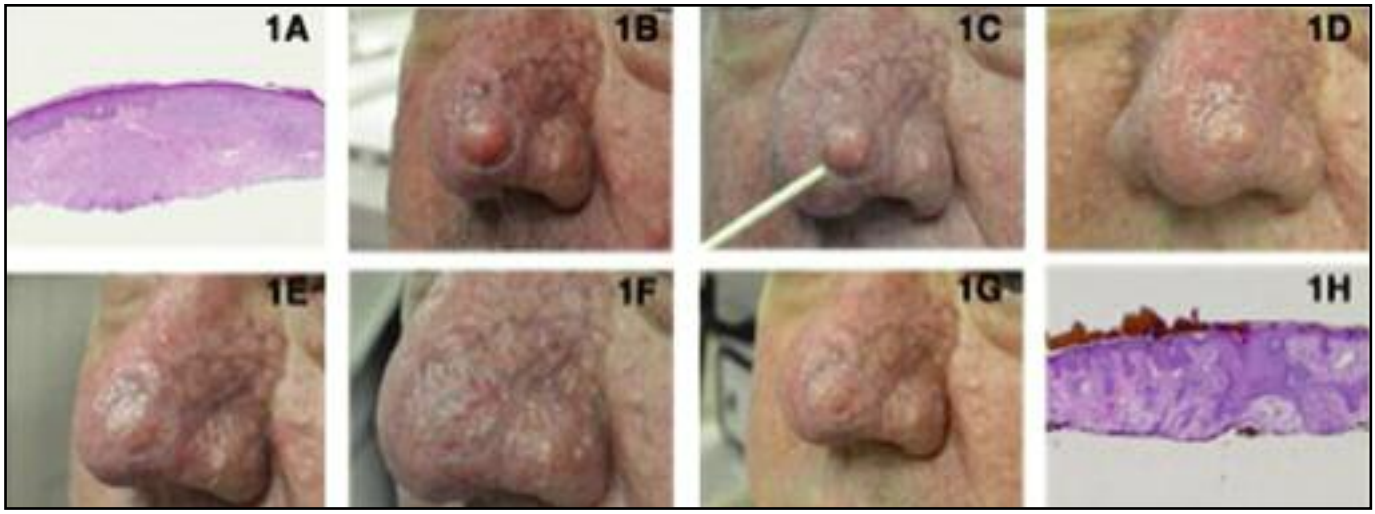

Figure 1. Assessment of extensive, infiltrative basal cell tumor on the nasal tip throughout nonsurgical treatment. (A) Initial biopsy before treatment shows multiple nests of basaloid cells in the dermis, consistent with extensive basal cell carcinoma; (B) lesion before treatment three months after baseline biopsy; (C) lesion three months after imiquimod treatment showing total regrowth of the tumor; (D) and (E) images of lesion three and six months into vismodegib treatment, respectively, show progressive clinical regression; (F) image of lesion three months post completion of vismodegib treatment shows no clinical evidence of tumor; (G) and (H) images of lesion six months post completion of vismodegib therapy appears resolved clinically and H&E, respectively. A repeat deep shave biopsy after treatment reveals mild dermal fibrosis and chronic inflammation, but no evidence of residual BCC.

nonmelanoma skin cancers (NMSC).[8,9,11,13,15] The OCT diagnostic sensitivity and specificity for NMSC varies by study, but ranges from 79 to 94 percent and 85 to 96 percent, respectively, whereas the clinical diagnostic sensitivity and specificity for NMSC ranges from 56 to 90 percent and 75 to 90 percent, respectively.[12,14,15] Regardless of the reported sensitivities and specificities, these studies have all shown OCT to improve diagnostic accuracy. More recently, the diagnostic value of OCT, specifically for BCC, was demonstrated in a population of clinically challenging lesions.[15] OCT improved diagnostic certainty by a factor of four over clinical examination alone, and improved diagnostic accuracy by 50 percent.[15] With OCT imaging, 48 percent more BCCs were detected than by clinical examination alone, and sensitivity in this population increased from 62.9 to 92.9 percent.[15] As such, OCT offers a powerful diagnostic tool for NMSC and can be used to monitor lesion treatment progress.[12]

Nonsurgical treatment options for locally advanced or metastatic BCCs include vismodegib (Erivedge, Genentech-Curis), the first and only available oral hedgehog pathway inhibitor drug.[2,16–18] While this novel treatment is efficacious in treating metastasized, recurrent, and inoperable BCCs, adverse side effects such as nausea, vomiting, muscle cramps, decreased appetite, weight loss, and alopecia can preclude long-term use.[16,18] Furthermore, efficacy of vismodegib treatment has not been determined in organ transplant recipients. More established topical field treatments, such as imiquimod 5% cream (Aldara, 3M Pharmaceuticals), have been shown to be effective treatments for superficial and nodular BCCs in the immunosuppressed population.[20]

Herein, the authors present an immunocompromised transplant recipient monitored noninvasively with OCT imaging to assess tissue morphology throughout nonsurgical combination therapy with oral vismodegib and imiquimod cream. To their knowledge, there is limited literature on the use of vismodegib in transplant patients, and this is the first reported case of its combination with imiquimod cream for advanced BCC in an immunosuppressed transplant patient that shows complete lesion clearance.

CASE REPORT

A 54-year-old Caucasian male transplant patient was referred to the authors' institution for noninvasive management of a large, cosmetically challenging biopsy proven BCC (Figures 1A and 1B). His medical history included type I diabetes mellitus, kidney and pancreas transplants in 1998, a subsequent kidney transplant in 2010, as well as a heart bypass surgery in 2005. The patient's medication regimen included prednisone (5mg daily) and mycophenolate mofetil (1000mg twice daily).

On the authors' initial evaluation, the patient presented with a clinically prominent 1cm pearly nodule on the nasal tip characteristic of BCC (Figure 1B), in addition to underlying rosacea resulting in rhinophymatous changes of the nose. Extensive tumor involvement throughout his nose was evident on noninvasive OCT imaging (Figure 2A). The OCT scans illustrated a clear lack of definition at the epidermal-dermal junction and variable-sized signal-poor ovoid structures in the dermis consisting of dark rims that spanned the entirety of the scan and measured to a depth of 2mm. These findings are characteristic of BCC and were consistent with the initial histopathological

interpretation of infiltrative, nodular basal cell nests from the referring institution three months prior. Surgical Mohs excision would likely necessitate a paramedian forehead reconstructive nose skin flap, and the patient was weary of the cosmetic outcome. As such, he came to the authors seeking an alternative, nonsurgical approach in place of the recommended Mohs surgery.

The patient began therapy with topical imiquimod (5%) cream (Aldara, 3M Pharmaceuticals) five times a week for six weeks. The patient reported a robust inflammatory response in the treatment area with an erythematous and crusted plaque on his nare and apparent resolution of his basal cell nodule. However, the tumor rapidly regrew following the completion of the regimen. Three months after the start of the imiquimod therapy, the patient's nasal tip appeared clinically unchanged (Figure 1C). After thorough discussion of the potential risks and benefits, the patient elected to begin oral vismodegib 150mg once daily. The patient reported several of the well-known adverse effects of muscle spasm, dysgeusia, alopecia, fatigue, and weight loss within two months of starting vismodegib treatment, but was motivated to continue treatment despite these side effects.[16]

Three months into vismodegib treatment, the lesion on the nasal tip appeared clinically resolved with no evidence of residual tumor (Figure 1D). Based on the current literature, the initial thought was to send the patient for Mohs surgery.[16] However, the respective OCT scans revealed evidence of multiple remaining tumor islands with decreased depth of about 1mm (Figure 2B). More extensive OCT imaging of the patient's nasal bridge and left nasal ala also revealed evidence of basal cell tumor with decreased definition in the dermal-epidermal junction and multiple signal-poor ovoid structures suggestive of actively necrosing basal cell (Figures 3A and 4A). Based on these findings, oral vismodegib was continued for an additional three months at the same dose.

At the completion of the second three-month course of vismodegib, the patient presented to us again with no clinical evidence of tumor on any location of his nose (Figure 1E). Yet, noninvasive imaging still showed a small residual focal signal poor ovoid tumor nest measuring less than 0.5mm in depth with preservation of the epidermal-dermal junction (Figure 2C). The other nasal locations showed no residual evidence of BCC (Figures 3B and 4B). Given the substantial improvement, the authors felt the remaining lesion would respond well to another course of topical therapy and the patient began imiquimod 5% cream five times a week for six weeks.

Three months later, the patient showed no presence of basal tumor nests on both clinical and OCT evaluation (Figures 1F and 2D). Specifically, OCT scans displayed features of multiple dilated vessels consistent with the patient's underlying rosacea and rhinophymatous changes of the nose. Given the extensive vasculature, there was concern that small tumor islands may be masked and an additional round of imiquimod therapy was advised. The patient reported developing a minimal reaction to this second round of imiquimod treatment with very mild redness and no crusting on his nare.

At his next visit three months later (12 months post the

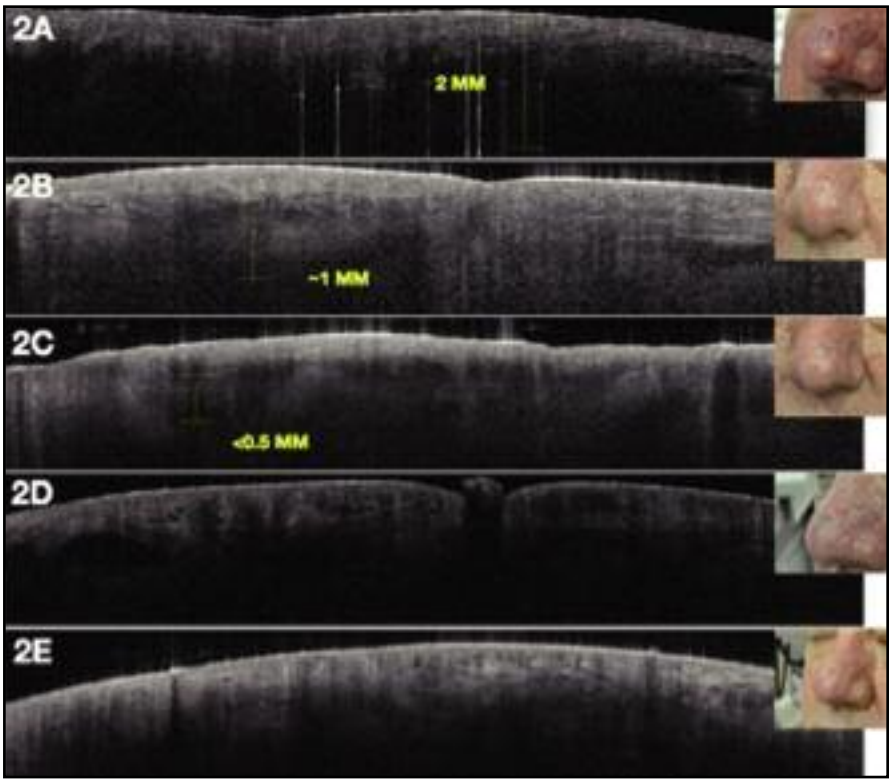

Figure 2. Noninvasive OCT assessment of extensive, infiltrative BCC on the nasal tip throughout nonsurgical treatment. (A) Prior to treatment, OCT image shows characteristic features of BCC, such as variable-sized signal-poor ovoid structures in the dermis with black rims and a white surrounding band that span the entirety of the scan and measure 2mm deep. A clear lack of definition at the epidermal-dermal junction is also observed; (B) three months into vismodegib, the OCT image reveals evidence of multiple tumor island structures, spanning a depth of about 1mm, characteristic of BCC; (C) six months into vismodegib, the OCT image shows evidence of a small focal, residual signal poor ovoid nest measuring less than 0.5mm in depth with preservation of the epidermal-dermal junction; (D) three months post vismodegib, OCT scans did not present with BCC island structures. These structures may be blurred (presumably because of inflammation) by the multiple dilated vessels; (E) six months post vismodegib, inflammation subsided and the OCT scans still display no ovoid BCC structures.

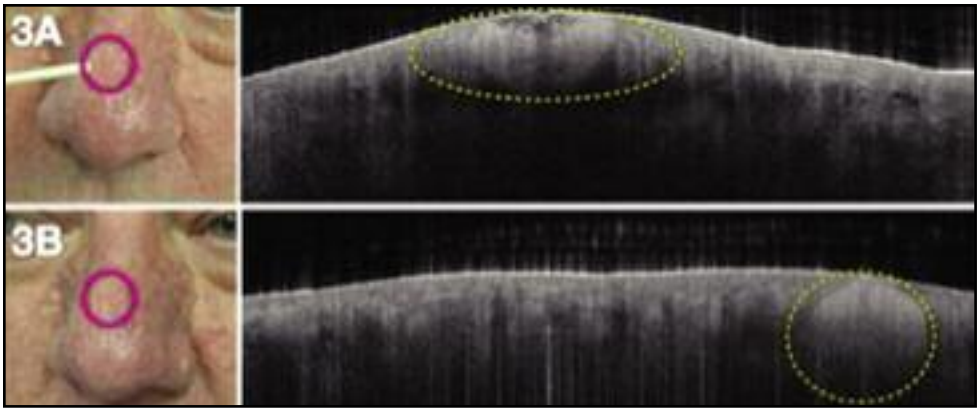

Figure 3. OCT imaging to identify and monitor BCC on bridge of nose. (A) Three months into vismodegib, the OCT image illustrates features suggestive of actively necrosing BCC with decreased definition in the dermal-epidermal junction and evidence of ulceration and ovoid structures with bright center; (B) six months into vismodegib, the OCT image shows no evidence of necrotic BCC tumor island structures.

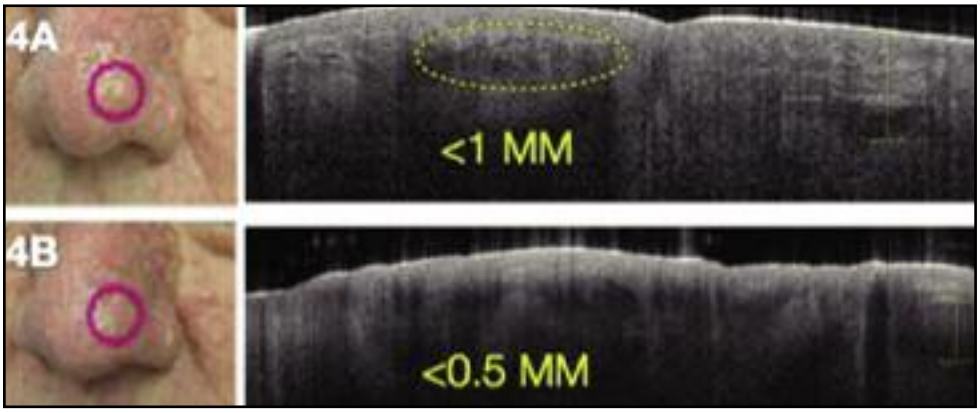

Figure 4. OCT imaging to identify and monitor BCC on left nasal ala. (A) Three months into vismodegib, the OCT image illustrates features suggestive of actively necrosing BCC with decreased definition of the dermal-epidermal junction and multiple signal-poor ovoid nests; (B) six months into vismodegib, the OCT image shows no evidence of necrotic BCC tumor island structures.

onset of vismodegib therapy), the patient again presented with complete resolution of basal tumor nests on both clinical and OCT evaluation (Figures 1G and 2E). A repeat deep shave biopsy of the nasal tip revealed mild dermal fibrosis and chronic inflammation with no evidence of residual BCC tumor (Figure 1H). After 21 months, the nare remains clinically clear of BCC and will continue to be followed clinically.

DISCUSSION

Management of advanced BCC in cosmetically sensitive areas presents a challenge to derm-atologists. Combined therapeutic strategies, such as vismodegib together with topical imiquimod, can help reduce the lesion size and make surgery and other noninvasive adjuvant therapies more feasible.

To date, there has been limited investigation of the risks and side effects of vismodegib specifically in transplant patients, and vismodegib remains largely restricted as a treatment option in this patient population.[7] This case report supports feasibility and efficacy of vismodegib for the treatment of facial BCCs in complicated renal transplant patients. Vismodegib worked with limited toxicity, however, adverse reactions to therapy suggest the need for individualized treatment schemes, as side effects may present even with short-term use.

Using ancillary noninvasive imaging tools, such as OCT, to monitor patients' treatment progress, especially when treatment is nonsurgical, provides dermatologists with many potential benefits. OCT seems to have the ability to noninvasively examine the gradual reduction of tumor size in real time, indicated by the decrease in tumor island depth and span on imaging scans. Studies have shown that tumor clinical appearance does not always correlate with histologic cure.[16] Additionally, OCT can be used to identify structures that are not visible or accessible to the naked eye, and thereby better determine therapeutic endpoints.

The current standard of care dictates that patients with residual BCCs based on clinical appearance after three to six months on vismodegib therapy should undergo surgical excision of tumor. In this case report, OCT was able to better assess the progress of treatment, with images exhibiting substantial basal cell involvement on the nasal tip and surrounding skin areas that appeared clinically clear. As such, an individually tailored endpoint of six months of oral therapy dictated by the use of OCT technology was established. Even after six months of vismodegib treatment, the patient still had a small focus of residual tumor on OCT, and the decision was made to use adjuvant topical therapy. The authors believe that the patient, at this point, could have had a good surgical outcome, suggesting the benefit of using vismodegib in combination with Mohs surgery or curettage too. The patient, however, opted to continue a nonsurgical treatment regimen that resulted in complete disease clearance and a very good cosmetic outcome.

CONCLUSION

The authors report a single case of effective treatment of an advanced BCC of the nose on an immunocompromised transplant patient using noninvasive technology to monitor the treatment progress of vismodegib and adjuvant imiquimod 5% cream therapies. Future studies will be needed to validate these results and assess the safety, efficacy, appropriate dosing regimen, and sustained clearance rates.

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REFERENCES

1. Kasper M, Jaks V, Hohl D, et al. Basal cell carcinoma—molecular biology and potential new therapies. *J Clin Invest*. 2012;122:45.
2. Fellner C. Vismodegib (Erivedge) for advanced basal cell carcinoma. *P T.* 2012;37:670–677.
3. Walling HW, Fosko SW, Geraminejad PA, et al. Aggressive basal cell carcinoma: presentation, pathogenesis, and management. *Cancer and Metastasis Review*. 2004;23(3-4):389–402.
4. Wheless L, Jacks S, Potter KAM, et al. Skin cancer in organ transplant recipients: More than the immune system. *J Am Acad Dermatol.* 2014;71:359–365.
5. Cowen EW, Billingsley EM. Awareness of skin cancer be kidney transplant patients. *J Am Acad Dermatol.* 1999;40:697–701.
6. Hartevelt MM, Bavinck JN, Kootle AM, et al. Incidence of skin cancer after renal transplantation in the Netherlands. *Transplantation.* 1980;49:506–509.
7. Cusack CA, Nijhawan R, Miller B, et al. Vismodegib for locally advanced basal cell carcinoma in a heart transplant patient. *JAMA Dermatology.* 2015;151:70–72.
8. Maier T, Braun-Faloc T, Hinz T, et al. Morphology of basal cell carcinoma in high definition optical coherence tomography: en-face and slice imaging mode, and comparison with histology. *J Eur Acad Dermatol Venereol*. 2013;27:e97–e104.
9. Ulrich M, von Braunmuehl T, Kurzen H, et al. The sensitivity and specificity of optical coherence tomography for the assisted diagnosis of non-pigmented basal cell carcinoma—an observational study. *Br J Dermatol.* 2015;173:428–435.
10. Tomlins PH, Woolliams P, Tedaldi M, et al. Measurement of the three-dimensional point-spread function in an optical coherence tomography imaging system. *Proc SPIE.* 2008;6847:68472Q.
11. Wahrlich C, Alawi SA, Batz S, et al. Assessment of a scoring system for basal cell carcinoma with multi-beam optical coherence tomography. *J Eur Acad Dermatol Venereol*. 2015;29:1562–1569.
12. Banzhaf CA, Themstrup L, Ring HC, et al. Optical coherence tomography imaging of non-melanoma skin cancer undergoing imiquimod therapy. *Skin Res Technol.* 2014;20:170–176.
13. Boone MA, Norrenberg S, Jemec B, et al. Imaging of basal cell carcinoma by high-definition optical coherence tomography: histomorphological correlation. A pilot study. *Br J Dermatol.* 2012;167:856–864.
14. Mogensen M, Joergensen TM, Nurmberg BM, et al. Assessment of optical coherence tomography imaging in the diagnosis of non-melanoma skin cancer and benign lesions versus normal skin: observer-blinded evaluation by dermatologists and pathologists. *Dermatol Surg.* 2009;35:965–967.
15. Markowitz O, Schwartz M, Feldman E, B et al. Evaluation of optical coherence tomography as a means of identifying earlier stage basal cell carcinomas while reducing the use of diagnostic biopsy. *J Clin Aesthet Dermatol.* 2015;8:14–20.
16. Ally MS, Asai S, Wysong A, et al. An investigator-initiated open-label clinical trial of vismodegib as a neoadjuvant to surgery for high-risk basal cell carcinoma. *J Am Acad Dermatol.* 2014;71:904–911.
17. Sofen H, Gross KG, Goldberg LH, S et al. A phase II, multicenter, open-label, 3 cohort trial evaluating the efficacy and safety of vismodegib in operable basal cell carcinoma. *J Am Acad Dermatol.* 2015;71:99–105.
18. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med*. 2012;366:2180–2188.
19. Lam T, Wolverton SE, Davis CL. Drug hypersensitivity syndrome in a patient receiving vismodegib. *J Am Acad Dermatol.* 2014; 70:e65–e66.
20. Vidal D, Alomar A. Efficacy of imiquimod 5% cream for basal cell carcinoma in transplant patients. *Clinical and Experimental Dermatology*. 2004;29:237–239.